

Translation

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference MS 001/2003 PCT	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/EP2003/005614	International filing date (<i>day/month/year</i>) 28 May 2003 (28.05.2003)	Priority date (<i>day/month/year</i>) 01 June 2002 (01.06.2002)
International Patent Classification (IPC) or national classification and IPC A61K 41/00		
Applicant MÜLLER-SCHULTE, Detlef, P.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
- ☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).
- These annexes consist of a total of 7 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 24 December 2003 (24.12.2003)	Date of completion of this report 10 September 2004 (10.09.2004)
Name and mailing address of the IPEA/EP	Authorized officer
Facsimile No.	Telephone No.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International appl. No.

PCT/EP2003/005614

I. Basis of the report

1. With regard to the elements of the international application:*

- ☐ the international application as originally filed
- ☒ the description:
 pages 1-35, as originally filed
 pages, filed with the demand
 pages, filed with the letter of
- ☒ the claims:
 pages 5-21, 22 (in part), as originally filed
 pages, as amended (together with any statement under Article 19
 pages, filed with the demand
 pages 22(in part),23-39,40(in part) // 1-4,40(in part),41-45, filed with the letter of 06.03.2004 // 30.08.2004
- ☐ the drawings:
 pages, as originally filed
 pages, filed with the demand
 pages, filed with the letter of
- ☐ the sequence listing part of the description:
 pages, as originally filed
 pages, filed with the demand
 pages, filed with the letter of

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item. These elements were available or furnished to this Authority in the following language which is:

- ☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of the translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages
- ☐ the claims, Nos.
- ☐ the drawings, sheets/fig

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rule 70.16 and 70.17).

** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.

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III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1-45 (in part)

because:

☒ the said international application, or the said claims Nos. 45
relate to the following subject matter which does not require an international preliminary examination (*specify*):

See the Supplemental Box.

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. _____
are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. _____ are so inadequately supported
by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claims Nos. 1-45 (in part)

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

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Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: III

1. An international search report was established only for the products indicated in the embodiments. Accordingly, the international preliminary examination report has been established only with respect to the subject matter for which a search has been carried out.
2. Claim 45 relates to subject matter that, in the opinion of the Examining Authority, comes under PCT Rule 67.1 (iv). Therefore, no written opinion has been established with respect to the industrial applicability of the subject matter of said claim (PCT Article 34(4)(a)(i)).

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International application No.

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V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-45	YES
	Claims		NO
Inventive step (IS)	Claims	1-45	YES
	Claims		NO
Industrial applicability (IA)	Claims	1-44	YES
	Claims		NO

2. Citations and explanations

3. This report makes reference to the following documents:

- D1: APPLIED MICROBIOLOGY AND BIOTECHNOLOGY 41, 1994, 99-105.
- D2: JOURNAL OF FERMENTATION AND BIOENGINEERING 84(4), 1997, 337-341.
- D3: BIOTECHNOLOGY PROGRESS., 17, No. 2, March 2001 (2001-03), 369-375
- D4: JOURNAL OF BIOMATERIALS SCIENCE, 11, No. 2, 2000, 123-147
- D5: WO 01/05586 A
- D6: WO 03/026618 A.

3.1 D1 discloses magnetic, thermosensitive polymers made of poly(styrene/N-isopropylacrylamide/methacrylic acid) latex particles containing magnetite. A structural change takes place owing to heating. Said document describes the use of said polymers for antibody purification. The production takes place in a two-stage process. D2 discloses polymers of this type, a temperature-dependent change in their structure, and their use for enzyme immobilization. Said document does not describe inverse dispersion

during production. D3 likewise discloses thermosensitive polymers containing N-isopropylacrylamide to which magnetite particles are added during polymerization and which show a temperature-dependent change in structure. The magnetism is used for faster sedimentation. The production takes place in a two-stage process.

- 3.2 D4 discloses thermosensitive polymers (poly(N-isopropylacrylamide/methacrylic acid)), their pH- and temperature-dependent structural changes, and their potential use as active substance carriers.
- 3.3 D5 discloses thermosensitive polymers (poly(N-isopropylacrylamide/methacrylic acid hydrogels)) containing metals (gold) which, when heated by means of electromagnetic radiation, lead to a structural change in the polymers, whereby active substances are released. Two-layer systems are described, and their use as microparticles is proposed (page 14).
- 3.4 D6 discloses thermosensitive particles (for example, made of thermosensitive polymers) treated with ultrasound in order to release active substances. Assuming a valid priority date, said document is not considered to be prior art for the purposes of the international preliminary examination.
4. The subject matter of claims 1-45 appears to be novel.
- 4.1 Claim 1 relates to thermosensitive polymers containing magnetic and/or metal colloids and characterized in that they can be produced by inverse suspension polymerization and in that their

physical structure can be changed by magnetic induction. D1-D3 and D5 disclose thermosensitive polymers that contain magnetic or metallic particles but are not produced by inverse suspension polymerization. Since, according to the applicant (see pages 13 and 14), the suspension polymerization influences the quality of the polymer articles, the subject matter of claims 1-24 appears to be novel.

4.2 Claims 25 and 26 relate to a method for producing thermosensitive polymers. Since none of documents D1-D5 discloses such a method, the subject matter of said claims appears to be novel.

4.3 Claim 43 relates to a method for releasing active substances by means of alternating magnetic fields, and claim 44 relates to a method for modifying the physical structure. Since none of documents D1-D5 discloses such a method, the subject matter of said claims appears to be novel.

4.4 Accordingly, claim 45, which relates to the use of these polymers in extremely different fields with the involvement of an alternating magnetic field, likewise appears to be novel.

5. Since none of documents D1-D5 discloses or renders obvious the use of alternating magnetic fields for releasing, the subject matter of claims 43 and 44 appears to be inventive. For the same reason, the subject matter of claims 1-42 and 45 appears to be inventive.

Patent claims

1. Thermosensitive polymers containing magnetic and/or metallic colloids, characterized in that their physical structure can be changed by magnetic induction or an energy supply.
2. Thermosensitive polymers containing magnetic and/or metallic colloids in accordance with Claim 1, characterized in that the polymers consist of poly-N-isopropylacrylamide, poly-N-substituted acrylamides, poly-N-substituted methacrylamides, copolymers of monomers from the group comprising N-isopropylacrylamide, N-substituted acrylamides and N-substituted methacrylamides, or mixtures of the aforementioned polymers or/and copolymers.
3. Thermosensitive polymers containing magnetic and/or metallic colloids in accordance with Claim 2, characterized in that the polymers contain one or more copolymers or block copolymers which apart from the monomer(s) mentioned contain one or more comonomers preferably selected from the group of monomers containing carboxyl groups, such as acrylic acid, methacrylic acid, or from acrylates, acrylate derivatives, methacrylates, methacrylate derivatives, acrolein, acrylamide, N-substituted acrylamides and vinyl acetate.
4. Thermosensitive polymers containing magnetic and/or metallic colloids in accordance with Claim 2 or 3, characterized in that the polymers contain one or more copolymers or block copolymers selected from the group comprising polyacrylic acid, polyacrolein,

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characterized in that the bonding groups are reacted with affinity ligands, peptides, proteins, antibodies, antigens, enzymes, cell receptor antibodies, antibodies against tumor markers, antibody fragments, artificially produced antibodies, modified antibodies, antibody conjugates, oligosaccharides, glycoproteins, lectins, nucleic acids, streptavidin or biotin.

23. Thermosensitive polymers containing magnetic and/or metallic colloids in accordance with one of Claims 1 to 22, characterized in that the polymers contain encapsulated active agents.
24. Thermosensitive polymers containing magnetic and/or metallic colloids in accordance with Claim 23, characterized in that the encapsulated active agents are selected from the group hormones, cytostatic agents, antibodies, antibody derivatives, antibody fragments, cytokines, immunomodulators, antigens, proteins, peptides, lectins, glycoproteins, nucleic acids, antisense-nucleic acids, oligosaccharides, antibiotics or generic agents.
25. Process for the production of thermosensitive polymers in accordance with one of Claims 1 to 24, characterized in that a monomer solution in which the magnetic and/or metallic colloids are dispersed is radically polymerized to a solid body through the addition of a multifunctional cross-linking agent and a radical initiator.
26. Process for the production of thermosensitive polymers in accordance with one of Claims 1 to 24, characterized in that an aqueous monomer solution in which the magnetic and/or metallic colloids are dispersed is suspended through mechanical comminution in an organic

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phase that is not miscible with water after adding a multifunctional cross-linking agent and a radical initiator and is radically polymerized to nano- or microparticles.

27. Process for the production of thermosensitive polymers in accordance with one of Claims 1 to 24, characterized in that an aqueous monomer solution in which the magnetic and/or metallic colloids are dispersed is suspended through mechanical comminution in an organic phase that is not miscible with water after adding a multifunctional cross-linking agent and is radically polymerized to nano or microparticles during the suspension process through the addition of a radical initiator.
28. Process for the production of thermosensitive polymers in accordance with one of Claims 25 to 27, characterized in that N-isopropylacrylamide, N-substituted acrylamides, N-substituted methacrylamides or mixtures of the same are used as a monomer.
29. Process for the production of thermosensitive polymers in accordance with one of the Claims 25 to 28, characterized in that 0.05 to 30 % by mol co-monomers are added to the monomer solution.
30. Process for the production of thermosensitive polymers in accordance with Claim 29, characterized in that the co-monomers are acrylate derivatives, methacrylate derivatives, acrylic acid, acrolein, methacrylic acid, acrylamide, vinyl acetate or mixtures of the same.
31. Process for the production of thermosensitive polymers in accordance with one of the Claims 25 to 30, characterized in that ferromagnetic, superparamagnetic

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or ferrimagnetic substances or low-temperature ferrites or ferrofluids with a particle size of $<1\text{ }\mu\text{m}$ are added to the monomer solution.

32. Process for the production of thermosensitive polymers in accordance with one of the Claims 25 to 31, characterized in that the ferromagnetic, superparamagnetic or ferrimagnetic substances or low-temperature ferrites are present as colloids or in a powder form.
33. Process for the production of thermosensitive polymers in accordance with Claim 26 or 27, characterized in that a nano or microparticle core polymer in which the magnetic and/or metallic colloids are dispersively encapsulated is added to the monomer solution.
34. Process for the production of thermosensitive polymers in accordance with Claim 33, characterized in that the core polymer is formed by chitosan, dextran, starch, polyacrylic acid, polysaccharides, silica gel, silicone derivatives, cellulose, proteins, albumin, polyacrylic acid, agarose, alginate, polystyrene, polyacrylates, polymethacrylates, polycyanoacrylates, polymethyl methacrylate, polyvinyl alcohol, polyamino acids, hyaluronic acid, polylactides, polyglycolides, polyacrolein or copolymers of the same.
35. Process for the production of thermosensitive polymers in accordance with Claims 26 and 27, characterized in that solvents used as the organic phase have a polar solubility parameter of $5-10\text{ (cal/cm}^3)^{1/2}$.
36. Process for the production of thermosensitive polymers in accordance with one of the Claims 26 and 27, characterized in that 0.05 to 15 % by weight of one or

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more surfactive substances is added to the organic phase.

37. Process for the production of thermosensitive polymers in accordance with Claim 36, characterized in that the surface active substance is from the group alkyl sulphosuccinates, polyoxyethylene aryl ethers, polyoxyethylenes, polyoxyethylene sorbitan esters, polyoxyethylene adducts, polyethylene propylene oxide block copolymers, alkylphenoxy polyethoxy ethanols, fatty alcohol polyethylene glycol ethers, polyglycerol esters, polyoxyethylene alcohols, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene acids and mixtures of the same.
38. Process for the production of thermosensitive polymers in accordance with Claim 26, characterized in that the monomer solution is pre-polymerized before dispersion in the organic phase for 5-120 seconds.
39. Process for the production of thermosensitive polymers in accordance with one of the Claims 25 to 38, characterized in that affinity ligands, peptides, proteins, antibodies, antigens, enzymes, cell receptor antibodies, antibodies against tumor markers, antibodies against tumor antigens, antibody fragments, artificially produced antibodies, modified antibodies, antibody conjugates, oligosaccharides, glycoproteins, lectins, nucleic acid, streptavidin or biotin are bonded to the polymers.
40. Process for the production of thermosensitive polymers in accordance with one of the Claims 25 to 39, characterized in that active agents are encapsulated in the polymers.

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ART 34 AND 1

41. Process for the production of thermosensitive polymers in accordance with Claim 40, characterized in that the active agents are selected from the group hormones, cytostatic agents, antibodies, cytokines, immunomodulators, antigens, proteins, peptides, lectins, glycoproteins, nucleic acids, antisense-nucleic acids, oligosaccharides, antibiotics and generic agents.
42. Process for the production of thermosensitive polymers in accordance with one of the Claims 40 or 41, characterized in that 0.1 to 20 % by weight of polyvalent alcohols, polyvinyl alcohols, gelatins or carbohydrates are added to the active agents.
43. Process for the production of thermosensitive polymers in accordance with Claim 42, characterized in that the polyvalent alcohols or carbohydrates are from the group inositol, mannitol, sorbitol, aldonol, erythritol, sucrose, glycerine, xylitol, fructose, glucose, galactose and maltose.
44. Process for the production of thermosensitive polymers in accordance with one of the Claims 40 to 43, characterized in that the encapsulated active agents are released as the result of magnetic induction or an energy supply.
45. The use of thermosensitive polymers containing magnetic and/or metallic colloids in accordance with one of the Claims 1 to 24 as contrast-intensifying media in NMR diagnostics, as carriers for active agents in medical therapy and diagnostics, as controllable carriers for reactants, as media to control microfluid processes, as separation media in column chromatography, as media to adjust and regulate pore sizes in membranes, as media to block blood vessels, as artificial cell

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carriers, as separation media for nucleic acids, cells, proteins, steroids, viruses or bacteria.

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